LA ROCHE POSAY
LABORATOIRE DERMATOLOGIQUE

ULTRA-LONG UVAs: AN INSIDIOUS ENEMY OF THE SKIN

LATEST SCIENTIFIC INFORMATION

LA ROCHE-POSAY, COMMITTED TO DERMATOLOGY

ULTRA-LONG UVAs: AN INSIDIOUS ENEMY OF THE SKIN

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1 INTRODUCTION TO UVA RAYS (320-400NM)

95% of UV rays are UVA. They are present all year round, have the capacity to pass through glass and clouds, and are persistent from sunrise to sunset. Ultraviolet A (UVA) radiation is immunosuppressive, mutagenic and carcinogenic in humans. UVA also causes an energy crisis in cells, and normalization of adenosine triphosphate with nicotinamide prevents UVA immunosuppression. UVA activation of the alternative complement pathway and defects in memory T-cell development are also involved. Human skin cancers contain mutations in the p53 and BRM genes that are consistent with being induced by UVA. The basal layer of human skin is more susceptible to UVA-induced mutations than the upper layers. Because skin cancers arise from these basal proliferating cells, this finding is likely to be important and could be attributable to low levels of the DNA repair enzyme OGG1 in basal cells. UVA suppresses immunity with a bell-shaped dose response. At doses equivalent to 15-20 minutes of sun exposure at noon, UVA contributes to approximately 75% of sunlight-induced immunosuppression[1].

2 UVA RAYS EFFECTS

ON SKIN

UVA not only contributes to the direct formation of DNA lesions but also impairs the removal of UV photoproducts from genomic DNA through oxidation and damage to DNA repair proteins. Alterations to the immune microenvironment by UVA-associated DNA damage responses may contribute to melanoma development [2].

UVA irradiation mainly triggers the formation of cyclobutane pyrimidine dimer (CPDs), especially CPD-TT both in cell models and in total human skin. A direct photochemical process is currently thought to account for CPD induction by UVA. The multilayer structure of the epidermis protects against UVB-induced dipyrimidine lesions in total skin but offers only weak protection against UVA. In addition, repair efficiency is undermined by UVA. UVA also mainly induces CPDs in melanocytes, in amounts like those observed in keratinocytes, demonstrating that melanin does not prevent CPD formation. In contrast, UVA induces far more abundant 8-oxo-Gua production in melanocytes than in keratinocytes. Thus, under UVA irradiation, oxidative stress contributes more to DNA damage in melanocytes than in keratinocytes[3].

Robust data also exists on the association between UVA and photo dermatoses[4]. Whole-body UVA exposure is a high-performance provocation test for both benign summer light eruption and polymorphous light eruptions patients although it cannot differentiate the two entities from one another[5].

ON THE IMMUNE SYSTEM

UVA is a major contributor to Solar-simulated ultraviolet radiation (SSUV)-induced immunosuppression at 72 h but only with the cooperation of UVB. Hence, UVB initiates immunosuppressive signals within 24 h, followed by UVA at 48 h, then an interaction between UVB and UVA. By 72 h following SSUV exposure, neither UVB nor UVA, but an interaction between them is the major cause of sunlight-induced immunosuppression. Sunlight-Induced Immunosuppression in humans is initially because of UVB, then UVA, followed by interactive effects on skin carcinogenesis[6].

3 INTRODUCTION TO LONG UVAS, UVA1 (340-400 NM)

Long UVAs (340-400nm) are known as UVA1. Among UVA1, ultra-long UVAs (380-400 nm) are known to be the most insidious. They form about 30% of total UV rays reaching our skin, go deep reaching the dermis, and their severe damages on the skin are not shown instantly but progressively with time. On reconstructed human skin model UVA1 induced immediate injuries such as generation of reactive oxygen species and DNA damage, accumulating preferentially in dermal fibroblasts and basal keratinocytes. UVA1 induced the modulation of expression of genes controlling cancer, proliferation, apoptosis and development, extracellular matrix and metabolism of lipids and glucose. Genes related to innate immunity and antiviral defense were severely repressed. These results suggest the consequences of UVA1 in photo-aging, photo-immunosuppression[7].

UVA1 induces early apoptosis or preprogrammed cell death through two apoptotic pathways in lymphocytes and immature proliferating mast cells[8]. The first pathway involves the production of superoxide anions and the second apoptotic pathway produces singlet oxygen species, which depolarize mitochondrial membranes[9]. UVA1 suppresses TNF-α, IL-12, IFN-γ, and ICAM-1.7-10 IL-6 and IL-8, cytokines with pivotal importance in sclerotic skin diseases, down regulated in localized scleroderma lesions[10].

UVA1 radiation suppresses calcineurin activity, both in vivo and in vitro. This loss in activity is due to singlet oxygen and superoxide generated by photosensitization. These findings provide a mechanistic basis for the hypothesis that UVA1 and calcineurin inhibitors both affect the same signal transduction pathway in the skin. UVA1 radiation inhibits calcineurin through oxidative damage mediated by photosensitization[11].

The effects of very long-wave UVA (>380 nm) and visible radiation (→400 nm) are much less known. UV/visible boundary wavelengths cause significant biologically relevant damage in vitro and in vivo, including dark CPD formation. This damage is most likely caused by oxidative stress generated by chromophores in the skin such as protoporphyrin IX, β-carotene and melanin that absorb strongly in this region. The UV/Visible Radiation Boundary Region (385-405 nm) Damages Skin Cells and Induces “dark” Cyclobutane Pyrimidine Dimers in Human Skin in vivo[12].

4 UVA1 RAYS EFFECTS

ON SKIN

A single UVA1 exposure induces an immediate and long-lasting skin darkening, with a similar amplitude in skin phototypes III to VI, together with a more pronounced grayish aspect in highly pigmented skins[13].

Selective staining for MMP1 (collagenase) and MMP12 (elastase) at 10 and 24 hours after one minimal erythema dose of UVA and UVB shows that UVA has a stronger effect than UVB on expression and activity of elastase at these times, while the opposite is true for collagenase. Preferential induction of elastase by UVA has implications for skin elasticity, as a result of elastin degradation, contributing to the effects of UVA on photoaging[14].

In human, UVA1 induces an immediate and persistent non-protective skin darkening and contributes to photoaging, immunosuppression and carcinogenesis[15].

A limited number of low-dose UVA1 exposures, as commonly experienced in daily life, potentially promotes photoaging by affecting breakdown, rather than synthesis, of collagen. Progressive skin darkening in response to repeated low-dose UVA1 exposures in lightly pigmented individuals does not prevent UVA1-induced collagenolytic changes[16].

ON THE IMMUNE SYSTEM

A recent action spectrum, indicating that 360-380 nm but not 320-350 nm UVA suppresses immunity in humans, suggests an important role for reactive oxygen species[17].

Longwave UVA, which abuts the visible light spectrum, is likely to be the largest contributor to immunosuppression resulting from incidental daily sun exposure[18].

UVA1-INDUCED CARCINOGENESIS

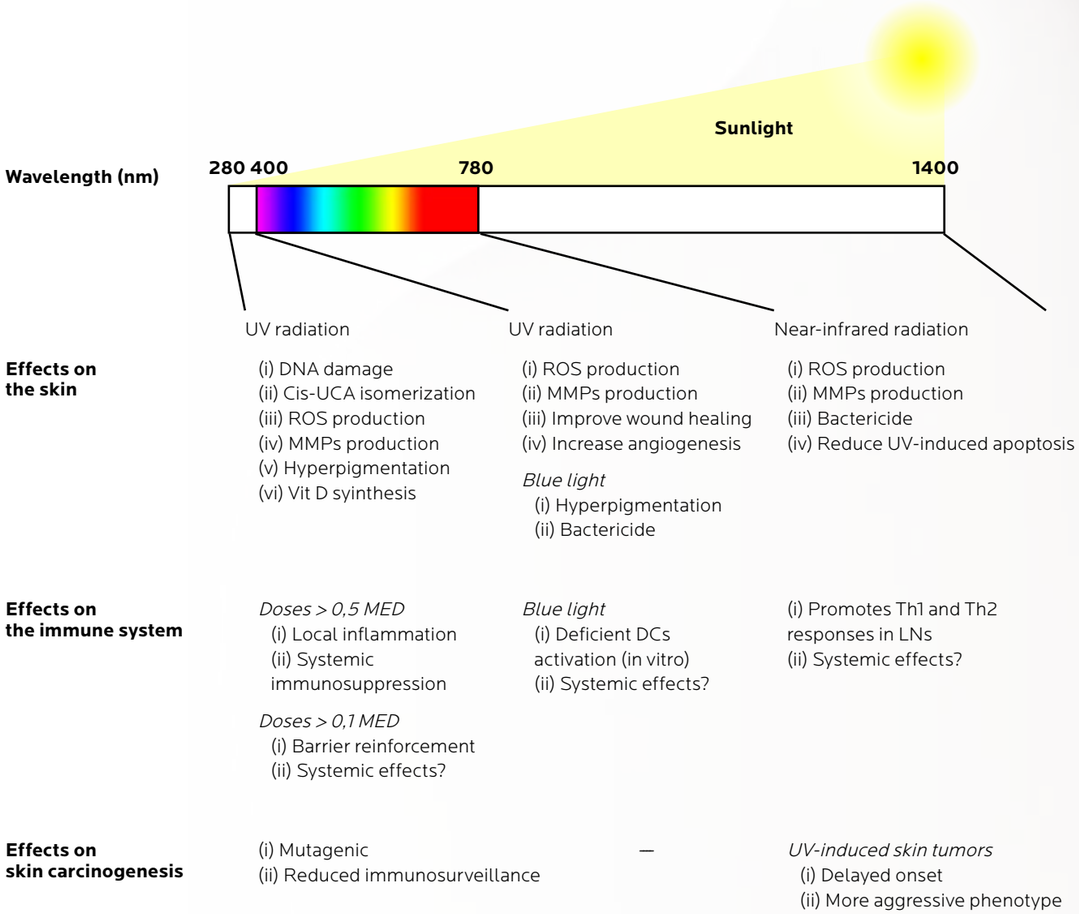
UVA1 may be more carcinogenic than has previously been thought. the number of cyclobutane pyrimidine dimers caused by long-wave UVA (UVA1, 340–400 nm) increases with epidermal depth, in contrast to attenuation seen with UVB (300 nm), demonstrating deeper damage with UVA. UVA1 induces thymine dimers (TTs), without pyrimidine (6-4) pyrimidone photoproducts (6-4PPs), in the epidermis, whereas UVB induced both photoproducts. UVB induced more TTs than UVA1 for the same level of erythema. The level of UVA1-induced TTs increased with epidermal depth in contrast to a decrease that was seen with UVB. UVA1- and UVB-induced TTs were repaired in epidermal cells at a similar rate. The mechanism by which UVA1 induces TTs is unknown, but a lack of intra-individual correlation between our subjects' UVB and UVA1 minimal erythema doses implies that UVA1 and UVB erythema occur by different mechanisms[19].

UVA1 has a specific ability to generate cyclobutane pyrimidine dimers (CPD), especially thymine dimers (T<>T), and that this is probably due to direct absorption of UVR. The CPD has been implicated in many aspects of skin cancer. Measuring UVB-induced CPD in the epidermis and dermis in vivo shows that, as expected, the skin attenuates UVB. In contrast, our data show that this is not the case with UVA1: in fact, there is more damage with increased skin depth[20].

Table 1: UV rays multi-targeted actions

	UVB (290–320 NM)	UVA (320-400 NM)	UVA LONG (340–400 NM)
On cells	Vitamin D production Oxidative Stress DNA damage	Oxidative Stress DNA damage	Mutagenesis Early Apoptosis Suppression of calcineurin activity Oxidative stress
On the skin	Increased sebum production Sunburn Erythema Delayed tanning Photosensitivity	Immediate and persistent pigment darkening Photosensitivity Photoaging (UVA) Photo dermatoses	Darkening
On the immune system	Immunosuppression	Immunosuppression	Immunosuppression
On skin carcinogenesis	Carcinogenesis	Carcinogenesis	Carcinogenesis By production of cyclobutane pyrimidine dimers TT

Figure 1: Sunlight effects on the skin and the immune system. The effects triggered by different wavebands of radiation are summarized, focusing on those effects described in the text. UCA: urocanic acid; ROS: reactive oxygen species; MMPs: matrix metalloproteases; MED: minimal erythema dose; DCs: dendritic cells; LNs: lymph nodes[21].



5 CONCLUSION

Despite the relative lack of awareness on UVA1, their noxiousness for the skin is real. Thus, dermatologists advocate not only a multi-pronged approach to minimizing sun exposure including lifestyle modifications, UVR protective clothing and sunglasses, but also a daily and topically application of sunscreen products with a high UVA-PF including protection against UVA1 up to 400 nm.

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